ClinicalTrials.gov ID **NCT03990051**

Treatment Safety and Efficacy of Pro-ocular™ 1% for Chronic Ocular Graft Following Allogeneic HSCT

Sponsor: **Glia, LLC**

Protocol

March 17, 2020

TREATMENT FOR CHRONIC OCULAR GRAFT-VERSUS-HOST DISEASE
- CLINICAL STUDY PROTOCOL -

Protocol Title:	Treatment safety and efficacy using Pro-ocular™ for chronic ocular graft versus host disease (GvHD) following allogeneic hematopoietic stem cell transplantation.
Study Objective:	To evaluate the safety and efficacy of Pro-ocular™ 1% topical gel administered twice daily for 70 days in ameliorating symptoms and signs of chronic ocular GvHD.
Version / Date:	V 5.1 March 17, 2020
Protocol Number:	oGvHD-1
Study Phase:	2
Study Drug and Placebo:	Pro-ocular™ 1% topical gel (progesterone) and placebo
IND Number:	143010
Indication:	Reduce or eliminate ocular symptoms and signs of chronic ocular graft-versus-host disease
Study Site:	Massachusetts Eye and Ear Longwood 800 Huntington Avenue Boston, MA 02115
Principal Investigator:	Zhonghui Katie Luo, MD, PhD
Co-Investigators:	Edwin P. Alyea III , MD Joseph H. Antin, MD Philippe Armand, MD, PhD Corey S. Cutler, MDCM, MPH Mahasweta Gooptu, MD Vincent Trien-Vinh Ho, MD John Koreth, MBBS, DPhil Sarah Nikiforow, MD, PhD Rizwan Romee, MD Robert J. Soiffer, MD
Sponsor:	Glia, LLC 134 Saint Botolph Street Boston, MA 02115
IRB:	Partners Human Research Committee

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SYNOPSIS

Protocol Title:	Treatment safety and efficacy using Pro-ocular™ for chronic ocular graft versus host disease (GvHD) following allogeneic hematopoietic stem cell transplantation
Version / Date:	V 5.1 March 17, 2020
Protocol Number:	oGvHD-1
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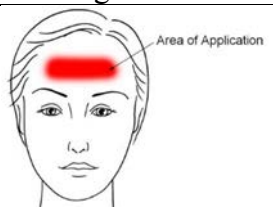
Study Drug and Placebo:	Pro-ocular™ 1% topical gel (progesterone USP) and placebo
IND Number:	143010
Indication:	Reduce or eliminate ocular symptoms and signs of chronic ocular graft-versus-host disease
Study Objective:	To evaluate the safety and efficacy of Pro-ocular™ 1% topical gel administered twice daily for 70 days in ameliorating symptoms and signs of chronic ocular GvHD.
Design Structure:	Single center, randomized, parallel, double-masked, placebo-controlled study
Institutional Review Board:	Partners Human Research Committee
Duration:	10-week treatment period (active and placebo) 6-week crossover period (placebo to active) open label phase long term phase to extend the entire treatment period for 27 months
Dosage/Dose Regimen:	Approximately 0.07 g Pro-ocular™ 1% topical gel applied and massaged into the forehead skin twice daily, morning and before bedtime.
Route of Administration:	
Visit Schedule, Double-Masked Phase:	5 visits over 70 days including: • Visit 1, Screening (Day -14 to -1) • Visit 2, Baseline and 1st drug application • Visit 3, 2-week follow-up (Day 14 ± 2) • Visit 4, 6-week follow-up (Day 42 ± 3) • Visit 5, 10-week follow-up (Day 70 ± 3)
Crossover Phase for Subjects on Placebo:	Subjects in placebo group will receive Pro-ocular 1% topical gel for twice daily administration for over 6 weeks starting at Visit 5:

	• Visit 6, 13-week follow-up (3 weeks on active drug), placebo cross-over subjects only • Visit 7, 16-week follow-up (6 weeks on active drug), placebo cross-over subjects only
Long Term Follow Up for Subjects in Open Label Phase (for Eligible & Interested Subjects)	Drug will be supplied after the study period for a total of 27 months' treatment period beginning with Visit 2, with safety monitoring and reporting by the PI and co-investigators under protocol during clinic: Visit 8, 66 ± 6 weeks (15 months) Visit 9, 117 ± 6 weeks (27 months)
Measures Taken to Reduce Bias:	Randomized treatment assignment; double-masked parallel study design, 2:1, study drug: placebo, 22 subjects:11 subjects
Number of Subjects:	33 patients diagnosed with chronic ocular GvHD in at least one eye, not wearing scleral or contact lens for at least one month in any eye prior to screening
Number of Study Sites:	1
Inclusion Criteria:	1. Male or female of any race, at least 18 years of age at Visit 1 Screening. 2. Has the diagnosis of chronic ocular GvHD. 3. Has the NIH Consensus Eye Score of at least 2. 4. On the GLIA Ocular Surface Disease Symptoms Questionnaire at Screening, has ocular discomfort at a severity score of moderate or more, and at least one other symptom at a severity of moderate or more. 5. One or more signs from the list of chronic ocular GvHD signs below. 6. Has provided verbal and written informed consent. 7. Be able and willing to follow oral and written instructions, including participation in all study assessments and visits.
Exclusion Criteria:	1. Wearing scleral lens within the last month, or those who plan to start wearing scleral lens during the study. 2. Anticipate major changes in systemic GvHD management during study period. 3. Comorbidity with other severe or chronic eye conditions that in the judgment of the investigator will interfere with study assessments, such as but not limited to retinal detachment, recent ocular surgery, Bell's palsy, active trigeminal neuritis or neuralgia.

	4. Anticipate change of vision correction or anticipate any ocular procedure during study period. 5. A woman who is pregnant, nursing an infant, or planning a pregnancy. 6. A woman of childbearing potential who has a positive urine pregnancy test at Visit 1, or who does not use an adequate method of birth control throughout the study period. 7. Has a known adverse reaction and/or sensitivity to the study drug or its components. 8. Unwilling to cease the use of sunscreen on the forehead or eye area. 9. Intraocular pressure >22 mm Hg at screening visit with or without ongoing glaucoma treatment. 10. Currently enrolled in an investigational drug or device study for ocular GvHD.
Evaluation Criteria:	
Efficacy Measures:	Glia Ocular Surface Disease Symptoms Questionnaire, Clinic and Daily Diary - Ocular discomfort - Dryness - Grittiness - Burning - Stinging - Foreign body sensation - Ocular pain - Conjunctival redness - Itching - Photophobia - Mucus discharge - Blurred or cloudy vision - Air flow sensitivity - Lid redness - Lid sticking Daily use of eye drops (Restasis®, Xiidra®, artificial tears and/or gels, autologous tears (# times administered per wake-time hours and sleep-time hours) SANDE – Symptom Assessment iN Dry Eye Questionnaire National Institutes of Health Eye Score Chronic ocular GvHD Signs (Ophthalmologist examination at each visit) - TearScan examination: Tear film, lid margins, and meibum expression

	- Visual acuity with current correction. - Slit lamp without staining: Lids (lid margin erythema, edema, ulceration, notches, entropion/ ectropion, trichiasis/madarosis, floppy eyelids, hordeolum); Conjunctiva (hyperemia, cicatricial changes, pseudomembranes, chalasis); Cornea (edema, ulcers, filamentous keratitis, thinning, corneal neovascularization, scars, conjunctival epithelium invasion, limbal thickening). - Corneal and conjunctival fluorescein staining Non-Ocular GvHD Signs (recorded by patient and physician): - Systemic assessment by BMT physician such as dry mouth
Safety Measures:	- Adverse events - Visual acuity - Slit lamp biomicroscopy - Undilated fundoscopy examination - Intraocular pressure - Systemic assessment by BMT physician at Dana Farber Cancer Institute
Laboratory Tests Routine and Afor Assessment of HPA (hypothalamic-pituitary-adrenal axis) Function	Tests to be run at Visits 1, 4, 5, 7, 8 and 9: Standard panel to include CBC with differential, metabolic panel, tacrolimus/sirolimus levels, Vitamin D Total 25-hydroxy (D2 and D3), T4 (T total and free), T3, ACTH, TSH, DHEA-S, estradiol, FSH, LH, progesterone, testosterone (total and free).

TREATMENT FOR CHRONIC OCULAR GRAFT-VERSUS-HOST DISEASE

CLINICAL STUDY PROTOCOL

Table of Contents

List of Abbreviations

ADL	Activities of daily living
AE	Adverse event
BID	Twice a day
BMT	Bone marrow transplantation
CN V	Cranial Nerve Five
CN VII	Cranial Nerve Seven
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum vitae
FDA	Food and Drug Administration
g	gram
GvHD	Graft-versus-host disease
HSCT	Hematopoietic stem cell transplantation
ICF	Informed consent form
IND	Investigational new drug application
IOP	Intraocular pressure
IRB	Institutional review board
ITT	Intent to treat
kg	kilogram
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
µg	microgram
mL	milliliter
µL	microliter
mm	millimeter
µm	micrometer
mmHg	millimeters of mercury
NCS	Not clinically significant
nd	not done
OD	Right eye
oGvHD	Ocular graft-versus-host disease
OS	Left eye
OU	Both eyes
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
USP	United States Pharmacopeia
VA	Visual acuity

TREATMENT FOR CHRONIC OCULAR GRAFT-VERSUS-HOST DISEASE - CLINICAL STUDY PROTOCOL

I. BACKGROUND AND SIGNIFICANCE

a. Historical background

Pro-Ocular™ topical gel has been studied in controlled clinical studies for dry eye, ocular discomfort and in compassionate use since 2013. Each metered dose of Pro-Ocular 1% will be about 0.07 g containing about 0.7 mg progesterone. One skin penetration study showed that less than 5% of the applied dose was able to cross the outer skin layer or stratum corneum.

b. Scientific evidence

The animal study done by Ian Meng et.al has just been published on Investigative Ophthalmology & Vision Science 2019; 60 (1706-1713). The study has shown that Progesterone 1% gel application to the forehead, but not the contralateral cheek of the rats, decreased pain sensation from capsaicin and hypertonic saline application. Local anesthesia of the forehead skin blocks the response. The work has indicated that the mechanism of action is not via systemic absorption; and a local neuro-pathway is likely activated to alter corneal nociception, likely via the cranial nerve V1 branch.

c. Previous pre-clinical or clinical studies leading up to, and supporting the proposed research

A product with a similar formulation, PG101 1% topical gel, was given to 24 subjects in a completed clinical trial for dry eyes under US IND 119774. A second group consisting of 24 subjects received PG101 0.25%. No drug related serious adverse events were reported. Adverse events with potential relationship to the topical gels in the completed study are approximately equal in placebo and treatment groups. The product demonstrated efficacy in multiple symptoms of dry eye disease such as ocular discomfort, dryness, and grittiness in both active arms as well as central corneal staining in the 1% active arm.

A study under US IND 123266 for ocular discomfort in glaucoma patients involving 0.5% topical gel enrolled approximately 40 subjects with no potential drug related serious adverse events reports. The study has not been unblinded for efficacy analysis.

Since late 2015 Pro-Ocular™ topical gel has been used by a total of 15 chronic ocular GvHD patients who had been suffering extreme ocular discomfort, with almost all encountering intractable ocular pain despite treatment with all available ocular drugs and devices such as BostonSight PROSE (prosthetic replacement of the ocular surface ecosystem). For most patients relief in symptoms began with the first application, and greater relief ensued with additional use. Symptomatic improvements to various extend were achieved by all patients after several weeks. For those wearing scleral lens, daily discomfort during wear and accumulation of debris behind the lens was reduced or eliminated.

Topical gels of both concentrations have been prescribed and dispensed through an authorized compounding pharmacy to additional patients under care of ophthalmologists. The prescribing physicians reported no serious treatment-related adverse events.

The same active ingredient, progesterone USP, occurs naturally in the human body, male and female, and can reach levels as high as100-200 ng/mL during late pregnancy. It is administered

at high doses in marketed FDA-approved products orally (200-400 mg/day), vaginally (300-800 mg/day), intramuscularly (up to 10 mg/day), and topically in marketed supplements (up to 80 mg/day). Both progesterone prescription products and marketed supplements are used chronically.

Progesterone is also found in foods such as eggs, dairy, yams, beans and dark green leafy vegetables.

c. Rationale behind the proposed research, and potential benefits to patients and/or society

A controlled study is necessary to verify findings in isolated patients, and is required for product to be approved by the Food and Drug Administration in order that the product can be made available to other patients. Currently available ophthalmic solutions and suspensions, drugs and devices have not been effective in alleviating the suffering of the ocular GvHD patients. Thus this is an unmet need that Pro-Ocular™ topical gel can fulfill.

Potential benefits: Decrease or cessation of adverse ocular symptoms and signs to regain quality of life, and prevention of ocular disease progression.

II. SPECIFIC AIMS

To evaluate the safety and efficacy of Pro-Ocular™ 1% topical gel administered twice daily for 70 days in ameliorating symptoms and signs of chronic ocular GvHD.

III. SUBJECT SELECTION

The plan is to screen 42 patients in order to achieve a study completion of 33 patients, 2:1 active drug:placebo. Subjects at least 18 years of age with a diagnosis of chronic ocular GvHD and fulfilling certain inclusion and exclusion criteria will be eligible. We anticipate that Dr. Luo, Principal Investigator, Ophthalmologist at MEE Longwood will have a sufficient number of eligible patients to enable enrollment from one site.

The inclusion and exclusion criteria are as follows:

Inclusion Criteria:	1. Male or female of any race, at least 18 years of age at Visit 1 Screening. 2. Has the diagnosis of chronic ocular GvHD. 3. Has the NIH Consensus Eye Score of at least 2. 4. On the GLIA Ocular Surface Disease Symptoms Questionnaire at Screening, has ocular discomfort at a severity score of moderate or more, and at least one other symptom at a severity of moderate or more. 5. One or more signs from the list of chronic ocular GvHD signs below. 6. Has provided verbal and written informed consent.

	7. Be able and willing to follow oral and written instructions, including participation in all study assessments and visits.
Exclusion Criteria:	1. Wearing scleral lens within the last month, or those who plan to start wearing scleral lens during the study. 2. Anticipate major changes in systemic GvHD management during study period. 3. Comorbidity with other severe or chronic eye conditions that in the judgment of the investigator will interfere with study assessments, such as but not limited to retinal detachment, recent ocular surgery, Bell's palsy, active trigeminal neuritis or neuralgia. 4. Anticipate change of vision correction or anticipiate any ocular procedure during study period. 5. A woman who is pregnant, nursing an infant, or planning a pregnancy. 6. A woman of childbearing potential who has a positive urine pregnancy test at Visit 1, or who does not use an adequate method of birth control throughout the study period. 7. Has a known adverse reaction and/or sensitivity to the study drug or its components. 8. Unwilling to cease the use of sunscreen on the forehead or eye area. 9. Intraocular pressure >22 mm Hg at screening visit with or without ongoing glaucoma treatment. 10. Currently enrolled in an investigational drug or device study for ocular GvHD.

The definition of scoring from the NIH Consensus for ocular GvHD is as follows:

NIH Consensus: 2014 Diagnosis and Staging Working Group

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* **Yes** **No** **Not examined**	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS

IV. SUBJECT ENROLLMENT

a. Methods of enrollment

Dr. Luo will review the qualifications of her active chronic ocular GvHD patients to determine eligibility, and query the eligible patients via a phone call by Dr. Luo herself as to their interest in participation.

b. Procedures for obtaining informed consent

An informed consent form will be provided for eligible patients to review. Dr. Luo herself will obtain the informed consent with each subject.

c. Treatment assignment, and randomization

Randomized double-masked parallel treatment assignment will be made using a block design at the ratio of 2:1, study drug:placebo, 22:11.

V. STUDY PROCEDURES

The sequence of procedures at each clinic visit is as follows:

Visit 1 (Day -14 to -1) **Screening**
Ophthalmology assessment
Informed consent by investigator
2-digit subject ID number
GLIA Ocular GvHD symptoms questionnaire
SANDE symptoms questionnaire
NIH Ocular GvHD score
Visual acuity with current correction
Slit-lamp biomicroscopy
Undilated fundoscopy exam
Corneal and conjunctival staining
Intraocular pressure
Urine pregnancy testing (as needed)
Inclusion/Exclusion criteria

Screening Pass or Fail by investigator Subject assigned 3-digit randomization code Review medical records for medical & ocular history Review prior and current medications Demographics
BMT (DFCI) physician systemic evaluation History Physical Concomitant medications Laboratory tests, standard & endocrine panel GvHD assessment
⇓
Visit 2 (Day 1) **Baseline & First Drug Application**
Medical/ocular update Medication update Facial photo 1 minute video of face and eyes (+ blink interval) TearScan examination GLIA Ocular GvHD symptoms questionnaire Dispense study drug by investigator STUDY DRUG APPLICATION by investigator 30-90 minutes' wait from application 1 minute video of face and eyes (+ blink interval) TearScan examination Adverse event query GLIA Ocular GvHD symptoms questionnaire Dispense daily diary and ocular medication log
⇓
Visit 3 (Day 14 ± 2), 2 weeks' treatment
Medical and medication update Diary and ocular medication log collection & compliance Drug collection & accountability 1 minute video of face and eyes (+ blink interval) TearScan examination Adverse event query SANDE symptoms questionnaire GLIA Ocular GvHD symptoms questionnaire Slit-lamp biomicroscopy Corneal and conjunctival staining Study drug, daily diary and ocular medication log dispensed
⇓
Visit 4 (Day 42 ± 3), 6 weeks' treatment
Ophthalmology assessment
Medical and medication update Diary and ocular medication log collection & compliance

Drug collection & accountability 1 minute video of face and eyes (+ blink interval) TearScan examination Adverse event query SANDE symptoms questionnaire GLIA Ocular GvHD symptoms questionnaire Slit-lamp biomicroscopy Corneal and conjunctival staining Study drug, daily diary and ocular medication log dispensed
BMT(DFCI) physician systemic evaluation Standard lab tests, GvHD assessment
⬇
Visit 5 (Day 70 ± 3), 10 weeks' treatment
Ophthalmology assessment
Visual acuity Medical and medication update Diary and ocular medication collection & compliance Drug collection & accountability Urine pregnancy test if applicable Facial photo 1 minute video of face and eyes (+ blink interval) TearScan examination Adverse event query SANDE symptoms questionnaire GLIA Ocular GvHD symptoms questionnaire Slit-lamp biomicroscopy Undilated fundoscopy exam Corneal and conjunctival staining NIH Ocular GvHD score Intraocular pressure Urine pregnancy test End of study phase Reconfirm drug dispensing for Open label Phase Dispense diary, ocular medication log and drug to Placebo group
BMT (DFCI) physician systemic evaluation Concomitant medications Laboratory tests, standard & endocrine panel GvHD assessment
⬇
Visit 6, 13 weeks for Placebo group only
Medical and medication update Diary and ocular medication log collection & compliance Drug collection & accountability 1 minute video of face and eyes (+ blink interval) TearScan examination Adverse event query SANDE symptoms questionnaire

GLIA Ocular GvHD symptoms questionnaire Slit-lamp biomicroscopy Corneal and conjunctival staining
⬇
Visit 7, 16 weeks for Placebo group only
Facial photo Medical and medication update Diary and ocular medication log collection & compliance Drug collection & accountability 1 minute video of face and eyes (+ blink interval) TearScan examination Adverse event query SANDE symptoms questionnaire GLIA Ocular GvHD symptoms questionnaire NIH Ocular GvHD Score[1] Slit-lamp biomicroscopy Corneal and conjunctival staining Intraocular pressure
BMT (DFCI) physician systemic evaluation Concomitant medications Laboratory tests, standard & endocrine panel GvHD assessment
Long Term Follow Up for Subjects in Open Label Phase (for Eligible & Interested Subjects) Visit 8, 66 weeks ± 6 weeks (15 months)
Facial photo 1 minute video of face and eyes (+ blink interval) TearScan examination Adverse event query SANDE symptoms questionnaire GLIA Ocular GvHD symptoms questionnaire NIH Ocular GvHD Score Slit-lamp biomicroscopy Visual Acuity Undilated fundoscopy exam Corneal and conjunctival staining Intraocular pressure
BMT (DFCI) physician systemic evaluation Concomitant medications Laboratory tests GvHD assessment
Long Term Follow Up for Subjects in Open Label Phase (for Eligible & Interested Subjects) **Visit 9, 117 ± 6 weeks (27 months)**
Facial photo

[1] Added as protocol deviation to original protocol v4.

1 minute video of face and eyes (+ blink interval)
TearScan examination
Adverse event query
SANDE symptoms questionnaire
GLIA Ocular GvHD symptoms questionnaire
NIH Ocular GvHD Score
Slit-lamp biomicroscopy
Visual Acuity
Undilated fundoscopy exam
Corneal and conjunctival staining
Intraocular pressure
BMT (DFCI) physician systemic evaluation
Concomitant medications
Laboratory tests, standard and relevant panel
GvHD assessment

The evaluation criteria are as follows:

Efficacy Measures:	Glia Ocular GvHD Symptoms Questionnaire Clinic Daily Diary - Ocular discomfort - Dryness - Grittiness - Burning - Stinging - Foreign body sensation - Ocular pain - Conjunctival redness - Itching - Photophobia - Mucus discharge - Blurred or cloudy vision - Air flow sensitivity - Lid redness - Lid sticking Use of eye drops (Restasis®, Xiidra® , artificial tears and/or gels, autologous tears , # times administered per wake-time hours and sleep-time hours) SANDE – Symptom Assessment iN Dry Eye Questionnaire National Institutes of Health Eye Score Ocular GvHD Signs (physician examination at each visit) - TearScan examination: Tear film, lid margins, and meibum expression. - Visual acuity with current correction. - Slit lamp without staining: Lids (lid margin erythema, edema, ulceration, notches, entropion/ ectropion, trichiasis/madarosis, floppy eyelids, hordeolum); Conjunctiva (hyperemia, cicatricial changes, pseudomembranes, chalasis); Cornea (edema, ulcers, filamentous keratitis, thinning, corneal neovascularization, scars, conjunctivial epithelium invasion, limbal thickening). - Corneal and conjunctival fluorescein staining Non-Ocular GvHD Signs (recorded by patient and physician): - Systemic assessment by BMT physician such as dry mouth
Safety Measures:	- Adverse events - Visual acuity - Slit lamp biomicroscopy - Undilated fundoscopy examination - Intraocular pressure - Systemic assessment by BMT physician at Dana Farber Cancer Institute
Laboratory Tests Routine and for	Tests to be run at Visits 1, 4, 5, 7, 8, and 9: CBC with differential, metabolic panel, tacrolimus/sirolimus levels,

Assessment of HPA (hypothalamic-pituitary-adrenal axis) Function	Vitamin D Total 25-hydroxy (D2 and D3), T4 (Total and free), T3, ACTH, TSH, DHEA-S, estradiol, FSH, LH, progesterone, testosterone (total and free).

Laboratory tests will be performed at the Dana Farber Cancer Institute (DFCI) and the Brigham Research Assay Core, Brigham and Women's Hospital. As DFCI patients study subject will continue to be followed at DFCI by the MD that referred them to Mass Eye and Ear. In addition to their standard of care examinations the study subjects will undergo additional laboratory testing including:

- CBC with differential
- Metabolic panel
- Tacrolimus/sirolimus levels
- Vitamin D Total 25-hydroxy (D2 and D3)
- T4 (Total and free)
- T3
- ACTH
- TSH.
- DHEA-S
- Estradiol
- FSH
- LH
- Progesterone
- Testosterone (total and free).

These DFCI physicians will be co-investigators in the study and will review the laboratory tests outcomes to ensure the safety of the subjects.

A selection of the key questionnaires and examination procedures specific to oGvHD are shown in the **Appendix**.

VI. BIOSTATISTICAL ANALYSIS

Analysis Populations:

Intent-to-Treat Population

The intent-to-treat (ITT) population includes all randomized subjects. The efficacy analyses will be performed on the ITT population with Last Observation Carried Forward (LOCF) method for missing values. The efficacy variables may also be analyzed utilizing the ITT population with observed data only (i.e. without LOCF) to assess sensitivity.

Per-Protocol Population

The per protocol (PP) population excludes subjects with significant protocol deviations and excludes any incomplete subject data. Protocol deviations will be assessed by the clinical team, prior to database lock. Efficacy analyses will be performed on the PP population with observed data only.

Sample Size
33 subjects.

Efficacy Analyses
The continuous and ordinal efficacy variables collected at each visit (and time point, where relevant) will be summarized with number of observations (n), mean, standard deviation, median, minimum and maximum. Statistical inference testing will be conducted and the results will be utilized as additional descriptors of the data. Two-sample *t*-tests will be employed for continuous variables. Two-sample t-tests, Wilcoxon rank sum tests and analysis of covariance (ANCOVA) models adjusting for baseline will be employed for ordinal variables. For the ANCOVA models, treatment will be compared to the placebo. Pearson's chi-square or Fisher's exact tests (in the case of expected counts less than 5) will be employed for qualitative variables. Where appropriate, the change from baseline for each parameter will also be summarized using descriptive statistics.

The individual symptoms collected in the diary will be analyzed including all data across the 70-day treatment period, testing for a treatment effect using a generalized linear model that accounts for repeated measures with an unstructured correlation structure, including terms for diary day and the treatment-by-day interaction.

VII. RISKS AND DISCOMFORTS

Based on the clinical use of the drug within and outside of controlled studies, there are no known risks. The amount of the active progesterone is several hundred-fold lower than the current injectable, topical, and oral forms. Skin penetration studies by Sponsor using the Franz cell has shown that less than 5% of progesterone passes through the top layer of the skin (stratum corneum).

Use of other ocular medications can continue, concurrent with use of Pro-ocular.

VIII. POTENTIAL BENEFITS

a. Potential benefits to participating individuals

The potential benefits to participating individuals are reduction or elimination of ocular discomfort, especially the extreme pain experienced by many ocular GvHD patients, and ocular tissue damage repair, potentially preventing progression to when surgical procedures may be required.

Another potential benefit is the reduction of use of artificial tears and other eye drops that only provide temporary relief.

There is potential improvement of the overall quality of life, and enabling the return to normal daily living, sleep, work, and other activities.

b. Potential benefits to society

The study is expected to prove that the study drug fulfills an unmet need for ocular GvHD treatment.

IX. MONITORING AND QUALITY ASSURANCE

a. Independent monitoring of source data

The sponsor intends to provide independent monitoring to ensure all data are collected, and entered into a database accurately.

b. Safety monitoring

A Safety Management Plan is provided to clinical management personnel. A 24-hour telephone physician safety monitor line will be provided for the subjects to call.

c. Outcomes monitoring

Data will be analyzed by a third-party statistical group.

d. Adverse event reporting guidelines

All adverse events will be collected, whether potentially related or unrelated to study drug use. The adverse events will be categorized according to the latest version of MedDRA (Medical Dictionary for Regulatory Activities) using Common Terminology Criteria (CTCAE). The Safety Management Plan provides guidance for what is considered a serious adverse event, the forms to be completed in such cases, and when a serious adverse event needs to be reported to the FDA.

X. REFERENCES

Ocular Findings in Chronic GvHD

Reference	Ocular Changes Chronic GvHD
Amparo F et al. Corneal fluorescein staining and ocular symptoms but not Schirmer test are useful as indicators of response to treatment in chronic ocular GVHD. Ocul Surf. 2018 May 12. pii: S1542-0124(18)30040-5.	Corneal fluorescein staining and symptoms better indicators than Schirmer scores
Anderson NG, Regillo C Ocular manifestations of graft versus host disease. Curr Opin Ophthalmol. 2004 Dec;15(6):503-7.	"Ocular findings include keratoconjunctivitis sicca, pseudomembranous conjunctivitis, corneal ulceration and perforation, and microvascular retinopathy."
Berchicci L et al. Ocular chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation in an Italian referral center. Ocul Surf. 2018 Jul;16(3):314-321.	More than 50% developed chronic ocular GVHD after allogeneic HSCT. Meibomian gland dysfunction, conjunctival hyperemia, and conjunctival fibrosis were major findings.
Blecha C et al. Verification of the new grading scale for ocular chronic graft-versus-host disease developed by the German-Austrian-Swiss consensus conference on chronic GVHD. Ann Hematol. 2016 Feb;95(3):493-9.	"85% of patients suffered from functional impairment due to ocular cGVHD." Ocular tissue involved: Lacrimal glad dysfunction 100% Lids 89% Conjunctiva 96% Cornea 76%
Blecha C et al. Retinal Involvement in a Patient with Cerebral Manifestation of Chronic Graft-Versus-Host-Disease. Oncol Res Treat. 2015;38(10):532-4.	"2 years later, she complained of right-sided blurred vision and floaters; both eyes showed whitish circumscribed retinal infiltrations, cellular infiltration of the vitreous and mild bilateral optic disc edema. Oncological and neurological work-up ruled out infectious diseases and other GvHD manifestations. Symptoms and signs resolved under continued systemic IS, leaving pigmented retinal scars."
Busin M, Giannaccare G, Sapigni L, Testoni N, Leon P, Versura P, Campos E. Conjunctival and Limbal Transplantation From the Same Living-Related Bone Marrow Donor to Patients With Severe Ocular Graft-vs-Host Disease. JAMA Ophthalmol. 2017 Oct 1;135(10):1123-1125.	"To date, no treatment has proven to be effective for severe ocular graft-vs-host disease (GVHD) after allogenic hematopoietic stem cell transplantation that leads to conjunctivalization and keratinization of the cornea through damage of conjunctival goblet cells and limbal epithelial stem cells (LESCs). We report the outcomes of chimerism induced by transplantation from the same living-related bone marrow donor of conjunctiva and LESCs in 4 eyes of 2 patients with severe ocular GVHD."
Claes K, Kestelyn P Ocular manifestations of graft versus host disease following bone marrow transplantation. Bull Soc Belge Ophtalmol. 2000;(277):21-6.	"The ocular manifestations of Graft Versus Host Disease (GVHD) include keratoconjunctivitis sicca, cicatricial lagophthalmos, sterile conjunctivitis, corneal epithelial defects, corneal ulceration and melting."

Reference	Ocular Changes Chronic GvHD
Curtis LM et al. Predictive models for ocular chronic graft-versus-host disease diagnosis and disease activity in transplant clinical practice. Haematologica. 2015 Sep;100(9):1228-36.	Significant findings in ocular cGvHD patients: Visual acuity deficits and vision difficulty Corneal staining Meibomian glands plugged Lid margin swelling Lid margin erythema Lid margin tear film debris Conjunctival injection [hyperemia → pseudomembranous conjunctivitis] Conjuntival chemosis [swelling] Dry eye (Schirmer test and tear film breakup time not as valuable as indicators.)
Dierich-Ntoukas T [Clinical Signs of Ocular Graft-versus-Host Disease]. Klin Monbl Augenheilkd. 2015 May;232(5):647-51.	"It is not only associated with reduced quality of life because of dry eye symptoms but can also impair visual acuity and lead to blindness due to corneal complications. Patients with ocular GvHD are often resistant to therapy because of the severe dry eye disease and persistent inflammatory activity."
Eberwein P et al [Patient-Centred Care of Ocular Graft-vs-Host Disease in Germany]. Klin Monbl Augenheilkd. 2015 May;232(5):664-8.	"Ocular GvHD is a severe complication following allogenic blood stem cell transplantation leading to massive reduction in quality of life and ocular pathologies including corneal perforation."
Gama I et al. Chronic Ocular Graft vs Host Disease as a Serious Complication of Allogeneic Hematopoietic Stem Cell Transplantation: Case Report. Transplant Proc. 2015 May;47(4):1059-62.	"Bilateral corneal ulcers and ocular perforation, although not frequent, can occur in most extreme cases."
Giannaccare G et al. Ocular surface analysis in hematological patients before and after allogeneic hematopoietic stem cell transplantation: implication for daily clinical practice. Eye (Lond). 2017 Oct;31(10):1417-1426.	50 patients or 53% were diagnosed as dry eye sufferers prior to HSCT. The incidence increased 77% or 72 patients post HSCT. Significant changes post HSCT: OSDI, TFBUT, MGD score, conjunctival injection; not so much Schirmer's.
Karwacka E et all Pemphigoid-like ocular lesions in patients with graft-versus-host disease following allogeneic bone marrow transplantation. Transplant Proc. 2006 Jan-Feb;38(1):292-4.	Pemphigoid-like ocular lesions in addition to keratitis sicca were seen in patients with graft-versus-host disease.
Kim S et al. Changes of meibomian glands in the early stage of post hematopoietic stem cell transplantation. Exp Eye Res. 2017 Oct;163:85-90.	"A significant increase was seen in the upper eyelid post-HSCT meiboscore at 2 months and 3 months, and in the total eyelid meiboscore at 3 months.
Kim SK 2006 Update on ocular graft versus host disease. Curr Opin Ophthalmol. 2006 Aug;17(4):344-8.	"Ocular graft versus host disease is a common sequela of allogeneic hematopoietic transplantation affecting up to 80% of chronic graft versus host disease patients. Clinical features of ocular graft versus host disease encompass all parts of the eye, from the lid to the choroids, although ocular graft versus host disease is most commonly viewed as a disease of the ocular surface, with the conjunctiva and lacrimal gland most commonly affected."

Reference	Ocular Changes Chronic GvHD
Kusne Y et al Conjunctival subepithelial fibrosis and meibomian gland atrophy in ocular graft-versus-host disease. Ocul Surf. 2017 Oct;15(4):784-788.	"Clinical CSEF [conjunctival subepithelial fibrosis) may be an important sign of GVHD impact on the ocular surface and may be relevant in oGVHD severity assessment."
Lin X, Cavanagh HD Ocular manifestations of graft-versus-host disease: 10 years' experience. Clin Ophthalmol. 2015 Jul 3;9:1209-13.	"The most common presentations were keratoconjunctivitis sicca, cataract, blepharitis, ocular hypertension, and filamentary keratitis. Visual acuity at presentation was 20/49; at the worst point in the disease was 20/115; and at most recent visit was 20/63."…"…they are prone to serious ocular complications such as corneal perforation and endophthalmitis."
Nassar A et al. Ocular manifestations of graft-versus-host disease. Saudi J Ophthalmol. 2013 Jul;27(3):215-22.	"Eyelid changes may occur in GVHD leading to scleroderma-like changes. Patients may develop poliosis, madarosis, vitiligo, lagophthalmos, and entropion. The cornea may show filamentary keratitis, superficial punctate keratitis, corneal ulcers, and peripheral corneal melting which may lead to perforation in severe cases. Scleritis may also occur which can be anterior or posterior. Keratoconjunctivis sicca appears to be the most common presentation of GVHD. The lacrimal glands may be involved with mononuclear cell infiltration of both the major and accessory lacrimal glands and decrease in tear production. Severe dry eye syndrome in patients with GVHD may develop conjunctival scarring, keratinization, and cicatrization of the conjunctiva."
Ogawa Y et al. Dry eye as a major complication associated with chronic graft-versus-host disease after hematopoietic stem cell transplantation. Cornea. 2003 Oct;22(7 Suppl):S19-27.	Ocular complications were listed for "chronic phase" Dry eye Meibomian gland dysfunction Retinal hemorrhage Aseptic conjunctivitis Lagophthalmos [inability to close eyelids completely] Corneal thinning Corneal melting Nasolacrimal obstruction Calcerous corneal degeneration Iritis Optic disc edema Cotton wool spots [fluffy white patches on retina] Cataract
Ogawa, Y. Sjögren's Syndrome, Non-Sjögren's Syndrome, and Graft-Versus-Host Disease Related Dry Eye. Invest. Ophthalmol. Vis. Sci. 2018;59(14):DES71-DES79.	"In most cases [of chronic ocular GvHD] severe dry eye progresses rapidly after the onset of symptoms and can lead to blindness. Despite improvements in the therapy for acute GVHD, specific therapies remain a substantial problem with little progress…Glaucoma, cataract, infection, and corneal perforation should be prevented as side effects that occur after topical or systemic corticosteroid administration for preventing or treating GVHD…The 2014 NIH diagnostic criteria stated ocular cGVHD as a new onset of dry eye in the post-transplant patient. Additional symptoms may include photophobia, periorbital hyperpigmentation, or blepharitis.

Reference	Ocular Changes Chronic GvHD
	Examination by ophthalmologists is necessary for diagnostic confirmation of keratoconjunctivitis sicca, cicatricial conjunctivitis, or punctate keratopathy. Schirmer's test was removed from the 2014 NIH diagnostic criteria."
Qiu Y et al. Manifestation of clinical categories of ocular graft-versus-host disease. J Ophthalmol. 2018 Aug 8;2018:6430953.	Acute ocular GVHD predicts chronic ocular GVHD, is typified by acute conjunctivitis, increased mucus eye secretions, red eye, and lacrimation. Chronic ocular GVHD signs beyond severe eye include corneal lesions such as filamentary keratitis, corneal ulcer, and corneal vascularization, pseudomembrane formation, corneal epithelium loss.
Saboo US et al. Vision-Related Quality of Life in Patients with Ocular Graft-versus-Host Disease. Ophthalmology. 2015 Aug;122(8):1669-74.	"Compared with healthy subjects, patients with ocular GVHD reported reduced scores on all NEI-VFQ-25 subscales (each $P < 0.001$) with the exception of color vision ($P = 0.11$)."… "Patients with ocular GVHD experience measurable impairment of vision-related QOL."
Shikari H et al. Onset of ocular graft-versus-host disease symptoms after allogeneic hematopoietic stem cell transplantation. Cornea. 2015 Mar;34(3):243-7.	Schirmer score can be "unreliable". Proposed reliance on incorporation of ophthalmological examination in BMT patients.
Shikari H et al. Ocular graft-versus-host disease: a review. Surv Ophthalmol. 2013 May-Jun;58(3):233-51.	Offers grading in acute and chronic GVHD. TABLE 1 *Conjunctival Grading in Acute and Chronic GVHD* Classification of Conjunctivitis in Acute GVHD[66] 0. None 1. Hyperemia 2. Hyperemia with serosanguinous discharge 3. Pseudomembranous conjunctivitis 4. Pseudomembranous conjunctivitis with corneal epithelial sloughing Classification of Conjunctivitis in Chronic GVHD[135] 0. None 1. Hyperemia 2. Palpebral conjunctival fibrovascular changes with or without epithelial sloughing 3. Palpebral conjunctival fibrovascular changes involving 25–75% of total surface area 4. Involvement of >75% of total surface area with or without cicatricial entropion "Cicatricial conjunctival changes (Table 1) and superior limbic keratoconjunctivitis are commonly seen in chronic ocular GVHD. There is associated palpebral and fornicial conjunctival symblepharon with consequent lid scarring and disturbed lid anatomy (ectropion, entropion, meibomian gland atrophy, and punctal stenosis)… Secondary epithelial changes such as punctate keratopathy develop with the formation of corneal filaments and painful erosions with resultant secondary infections, non-healing ulcerations, and corneal perforations." "KCS has been observed in 69--77% of patients with chronic systemic GVHD and is an early sign of systemic involvement in extensive chronic GVHD."
Siebelmann S et al.	"Potential complications include visual loss, pain and damage to the ocular structures with, e.g. corneal

Reference	Ocular Changes Chronic GvHD
[Non-Invasive Diagnosis of Ocular Graft-versus-Host Disease]. Klin Monbl Augenheilkd. 2015 May;232(5):652-7.	ulcerations….. Available tests are mostly evaluated for usage in dry eye diagnosis but are, however, mostly unspecific for diagnosing ocular GvHD reliably."
Sun YC et al. Impact of Ocular Chronic Graft-versus-Host Disease on Quality of Life. Biol Blood Marrow Transplant. 2015 Sep;21(9):1687-91.	"Of the 284 chronic GVHD patients, 116 (41%) had ocular GVHD within 3 months of chronic GVHD diagnosis ("early ocular GVHD"). Late ocular GVHD (new onset > 3 months after chronic GVHD diagnosis) occurred in 64 patients. Overall cumulative incidence at 2 years was 57%."
Tung CI Graft versus host disease: what should the oculoplastic surgeon know? Curr Opin Ophthalmol. 2017 Sep; 28(5):499-504.	"Ocular GVHD occurs as a common immune-mediated complication of hematopoietic stem cell transplantation that presents as a Stevens-Johnson-like syndrome in the acute phase or a Sjögren-like syndrome in the chronic phase. Cicatricial conjunctivitis may be underreported in ocular GVHD. The spectrum of oculoplastic manifestations includes GVHD of the skin, cicatricial entropion, nasolacrimal duct obstruction, and lacrimal gland dysfunction. Surgical treatment is indicated for patients with significant corneal complications from entropion. Surgical approach to repair of nasolacrimal duct obstruction is presented in this review, including modified approaches for treating patients at risk for keratitis sicca."
Westeneng AC et al Ocular graft-versus-host disease after allogeneic stem cell transplantation. Cornea. 2010 Jul;29(7):758-63.	"Over time, ocular GvHD developed in 54% of patients and consisted mainly of dry eyes and conjunctivitis, which increased in severity during follow-up; blepharitis and uveitis were less often encountered….eye symptoms affecting activities of daily living were reported in 24 of 54 patients (44%) and 16 of 54 patients (30%) experienced temporary loss of visual acuity of more than 2 Snellen lines, only 1 developed permanent unilateral loss (counting fingers) because of ischemic vasculopathy."

APPENDICES

SCHEDULE OF VISITS AND ASSESSMENTS

Visits 1-7

Blue = Conducted at DFCI		Study Treatment Phase					Placebo Cross-over Phase	
Black = Conducted at MEEI	**Visit 1 (Screening)**	**Visit 2 Baseline & First Drug Application**		**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
	Day -14 to -1	**Day 1**	**Day 1**	**Day 14±2**	**Day 42±3**	**Day 70±3**	**3 weeks**	**6 weeks**
Procedure		**Pre-Dose**	**30-60 min Post-Dose**					
2-digit screening number	X							
Informed consent	X							
Visual acuity (current correction)	X					X		
NIH Ocular GvHD Score	X					X		X[2]
Facial photo		X				X		X
Slit lamp biomicroscopy	X			X	X	X	X	X
Undilated fundoscopy exam	X					X		
Corneal and conjunctival staining	X			X	X	X	X	X
Intraocular pressure	X					X		X
Inclusion/Exclusion criteria	X							
Medical/Ophthalmology history and updates	X	X		X	X	X	X	X
Prior and concomitant medication query	X	X		X	X	X	X	X
Concomitant medications (BMT)	X				X	X		X
Medical history & physical (BMT)	X							
Demographic data	X							
Video of face & eyes (1 minute)		X	X	X	X	X	X	X
TearScan examination		X	X	X	X	X	X	X
Urine pregnancy test	X					X		
Modified SANDE questionnaire	X			X	X	X	X	X
GLIA Ocular Surface Disease Symptoms Questionnaire	X	X	X	X	X	X	X	X
Adverse event query			X	X	X	X	X	X
Screen Pass/Fail	X							
3-digit random number	X							
BMT systemic evaluation & GvHD assessment	X				X	X		X
Standard GvHD, CBC, and metabolic labs	X				X	X		X
Endocrine panel	X				X	X		X
Daily diary and ocular medication log collected				X	X	X	X	X
Study drug collected/ accountability				X	X	X	X	X
Study drug application (in-clinic)		X						
Study drug dispensed		X		X	X	X	X	
Daily diary & ocular medication log dispensed			X	X	X	X	X	

[2] Added as protocol deviation to original protocol v4.

SCHEDULE OF VISITS AND ASSESSMENTS

Visits 8-9 Long Term Open Label

Blue = Conducted at DFCI	**Visit 8**	**Visit 9**
Black = Conducted at MEEI	**66 ± 6 weeks (15 months)**	**117 ± 6 weeks (27 months)**
Procedure		
Informed consent for long term open phase	X	X
Visual acuity (current correction)	X	X
NIH Ocular GvHD Score	X	X
Facial photo	X	X
Slit lamp biomicroscopy	X	X
Undilated fundoscopy exam	X	X
Corneal and conjunctival staining	X	X
Intraocular pressure	X	X
Ophthalmology updates	X	X
Concomitant medications (BMT)	X	X
Video of face & eyes (1 minute)	X	X
TearScan examination	X	X
Urine pregnancy test	X	X
Modified SANDE questionnaire	X	X
GLIA Ocular Surface Disease Symptoms Questionnaire	X	X
Adverse event query	X	X
BMT systemic evaluation & GvHD assessment	X	X
Standard GvHD, CBC, and metabolic labs	X	X
Endocrine panel	X	X

Initials: _____ Subject #:_____ Date: _____ Examiner: _____

Symptom Assessment iN Dry Eye (SANDE) Questionnaire

PLEASE COMPLETE THE FOLLOWING QUESTIONS REGARDING THE FREQUENCY AND SEVERITY OF YOUR DRY EYE SYMPTOMS.

1. Frequency of symptoms:

Please place an 'X' on the line to indicate how often, on average, your eyes feel **dry and/or irritated**:

Left Rarely _____ All the time

Right Rarely _____ All the time

2. Severity of symptoms:

Please place an 'X' on the line to indicate how severe, on average, you feel your symptoms of **dryness and/or irritation**:

Left Very Mild _____ Very Severe

Right Very Mild _____ Very Severe

GLIA™ OCULAR SURFACE DISEASE SYMPTOMS QUESTIONNAIRE - CLINIC RECORD

Initials: _____ Subject #: _____ Date: _____ Examiner: _____

Grade by placing X on the line from 'None' to 'Most severe' None _____ Most

	Baseline Time: _____		**Post-application 30-90 min Time:** _____	
	OD	**OS**	**OD**	**OS**
Ocular discomfort	None _____ Most	None _____ Most	None _____ Most	None _____ Most
Dryness	None _____ Most	None _____ Most	None _____ Most	None _____ Most
Grittiness	None _____ Most	None _____ Most	None _____ Most	None _____ Most
Burning	None _____ Most	None _____ Most	None _____ Most	None _____ Most
Stinging	None _____ Most	None _____ Most	None _____ Most	None _____ Most
Foreign body sensation	None _____ Most	None _____ Most	None _____ Most	None _____ Most
Ocular pain	None _____ Most	None _____ Most	None _____ Most	None _____ Most
Conjunctival redness	None _____ Most	None _____ Most	None _____ Most	None _____ Most

Additional notes below: (Details and other ocular symptoms)

GLIA™ OCULAR SURFACE DISEASE SYMPTOMS QUESTIONNAIRE - CLINIC RECORD

Initials: _____ Subject #: _____ Date: _____ Examiner: _____

Grade by placing X on the line from 'None' to 'Most severe' None _____ Most

	Baseline Time: _____		**Post-application 30-90 min Time:** _____	
	OD	**OS**	**OD**	**OS**
Itching	None _____ Most	None _____ Most	None _____ Most	None _____ Most
Mucus discharge	None _____ Most	None _____ Most	None _____ Most	None _____ Most
Photophobia	None _____ Most	None _____ Most	None _____ Most	None _____ Most
Blurred or cloudy vision	None _____ Most	None _____ Most	None _____ Most	None _____ Most
Airflow sensitivity	None _____ Most	None _____ Most	None _____ Most	None _____ Most
Lid redness	None _____ Most	None _____ Most	None _____ Most	None _____ Most
Lid sticking	None _____ Most	None _____ Most	None _____ Most	None _____ Most

Additional notes below: (Details and other ocular symptoms)

Ocular GvHD Evaluations & Scoring in clinic

Evaluation	Method	Scoring
Pre-fluorescein stain		
Visual acuity	Eye chart, OD and OS	See below
Slit lamp: Lids: Lid margin erythema, edema, ulceration, notches, entropion/ ectropion, trichiasis/madarosis, floppy eyelids, hordeolum; Conjunctiva: Hyperemia, cicatricial changes, pseudomembranes, chalasis; Cornea: Edema, ulcers, filamentous keratitis, thinning, corneal neovascularization, scars, conjunctivial epithelium invasion, limbal thickening; Anterior chamber: Cells, flare; Lens opacity	Visual or slit lamp	None — Most severe None — Most severe
Tear film evaluation + lid margin	TearScan	0,1, 2, 3
After fluorescein stain		
Fluorescein staining	Slit lamp	None — Most severe None — Most severe
Intraocular pressure	Applanation tonemetry	Reading in mm Hg

NIH Ocular GvHD Score

SCORE 0	SCORE 1	SCORE 2	SCORE 3
No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS

Tearscan™ Examinations

The TearScan enables non-invasive viewing of the lipid film on the surface of the eye that does not require the use of fluorescein staining. It provides a white light source that encircles the eye, to allow illumination of the ocular surface. A video camera inserted in the center of the ring of light, and connected to a computer, allows viewing and video recording of the tear film

During the examination, a one-minute video that includes 3 natural blinks should be recorded.

The grading will be from 0 to 3:

0 = no discernible tear film
1 = thin tear film
2 = moderate tear film
3 = copious tear film

Initials: _____ Subject #:_____ Date: _____ Examiner: _____

OD (right eye) Score: _____

OS (left eye) Score: _____

Red eye lid: Yes_____ No_____

Visual Acuity

Distance and near Snellen acuity in current glasses if wearing, (or no glasses if not wearing), then pinhole.

OD (right eye) _____

OS (left eye) _____

SLIT LAMP BIOMICROSCOPY WITHOUT STAINING – OCULAR GvHD

Initials: _____ Subject #:_____ Date: _____ Examiner: _____

Indicate a Grade by placing X on the line for all POSITIVE FINDINGS:

If finding present, Check NCS or CS (NCS = Non Clinically Significant CS = Clinically Significant)

Lids ☐ No positive findings	**OD**		**OS**	
Erythema	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Edema	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Lid margin ulceration	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Lid margin notches	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Entropion/Ectropion	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Trichiasis/Madarosis	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Floppy eyelids	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Hordeolum (stye)	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Other pathology, specify: ____		☐CS ☐NCS; ____		☐CS ☐NCS; ____ ☐CS ☐NCS
Conjunctiva ☐ No positive findings	**OD**		**OS**	
Hyperemia	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Cicatricial changes	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Pseudomembranes	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Chalasis	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Other pathology, specify: ____		☐CS ☐NCS; ____		☐CS ☐NCS; ____ ☐CS ☐NCS
Cornea ☐ No positive findings	**OD**		**OS**	
Edema	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Corneal ulcers	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Filamentous keratitis	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS

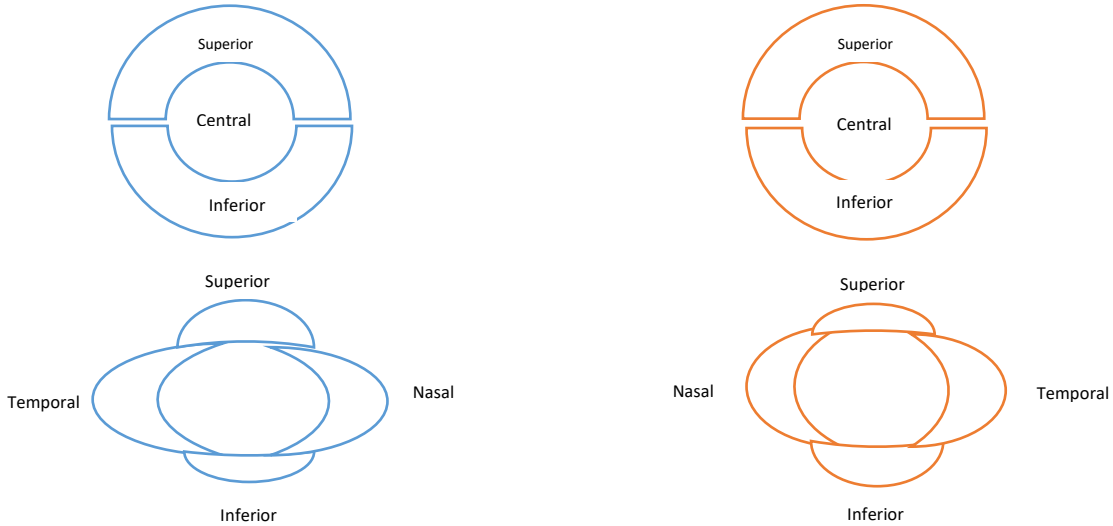
Indicate a Grade by placing X on the line for all POSITIVE FINDINGS:				
If finding present, Check NCS or CS (NCS = Non Clinically Significant CS = Clinically Significant)				
Corneal thinning	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Corneal neovascularization	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Scars	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Conjunctival epithelium invasion	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Limbal thickening	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Other pathology, specify: ____ ☐CS ☐NCS; ____ ☐CS ☐NCS; ____ ☐CS ☐NCS				
Anterior Chamber ☐ No positive findings	**OD**		**OS**	
Cells	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Flare	None ____ Most severe	☐CS ☐NCS	None ____ Most severe	☐CS ☐NCS
Other pathology, specify: ____ ☐CS ☐NCS; ____ ☐CS ☐NCS; ____ ☐CS ☐NCS				
Lens Status	**OD**		**OS**	
	☐Phakic ☐Pseudophakic ☐Aphakic		☐Phakic ☐Pseudophakic ☐Aphakic	
Lens Opacity (Phakic Eye ONLY) ☐ No positive findings	**OD**		**OS**	
	☐$_0$☐$_{+1}$☐$_{+2}$ ☐$_{+3}$	☐CS ☐NCS	☐$_0$☐$_{+1}$☐$_{+2}$ ☐$_{+3}$	☐CS ☐NCS
Comments:				

FLUORESCEIN STAINING

Initials: _____ Subject #:_____ Date: _____ Examiner: _____

Sodium Fluorescein strips (thin tipped, DET™ strips preferred) should be moistened with one or two drops of sterile irrigating or saline solution. Apply moistened tip to conjunctiva or fornix. The subject should blink several times after application and wait for 2 minutes before examination.

Indicate a Grade by placing X on the line for all POSITIVE FINDINGS:				
If finding present, Check NCS or CS (NCS = Non Clinically Significant CS = Clinically Significant)				
Cornea (C) ☐ No positive findings	**OD**		**OS**	
Inferior	None ——— Most severe	☐CS ☐NCS	None ——— Most severe	☐CS ☐NCS
Superior	None ——— Most severe	☐CS ☐NCS	None ——— Most severe	☐CS ☐NCS
Central	None ——— Most severe	☐CS ☐NCS	None ——— Most severe	☐CS ☐NCS
Other pathology, specify: _____ ☐CS ☐NCS; _____ ☐CS ☐NCS; _____ ☐CS ☐NCS				
Conjunctiva ☐ No positive findings	**OD**		**OS**	
Inferior	None ——— Most severe	☐CS ☐NCS	None ——— Most severe	☐CS ☐NCS
Superior	None ——— Most severe	☐CS ☐NCS	None ——— Most severe	☐CS ☐NCS
Temporal	None ——— Most severe	☐CS ☐NCS	None ——— Most severe	☐CS ☐NCS
Nasal	None ——— Most severe	☐CS ☐NCS	None ——— Most severe	☐CS ☐NCS
Other pathology, specify: _____ ☐CS ☐NCS; _____ ☐CS ☐NCS; _____ ☐CS ☐NCS				



UNDILATED FUNDOSCOPY – OCULAR GvHD

(To be performed only at Screening and Last Visit)

Initials: _____ Subject #:_____ Date: _____ Examiner: _____

Check Normal or Abnormal (If Abnormal, check CS or NCS)*	**OD**				**OS**			
	Normal	**Abnormal**		**Abnormal comments**	**Normal**	**Abnormal**		**Abnormal comments**
		NCS	**CS**			**NCS**	**CS**	
Vitreous	☐	☐	☐		☐	☐	☐	
Optic nerve	☐	☐	☐		☐	☐	☐	
Macula	☐	☐	☐		☐	☐	☐	
Vessels	☐	☐	☐		☐	☐	☐	
Cup to disc ratio								

URINE PREGNANCY TEST FOR WOMEN OF CHILDBEARING AGE

Urine Test Strip: HCG One Step Pregnancy Test or similar.

Urine Collection: A nurse will dispense a urine collection cup for urine collection.

Test Procedure: Follow directions, but usually the test strip is dipped into the urine for 3 seconds, and laid flat for reading within 5 minutes.

Initials: _____ Subject #:_____ Date: _____ Examiner: _____

CBC and DIFFERENTIAL	*Normal Range*
WBC	*3.81 - 8.94 K/uL*
RBC	*4.35 - 5.61 M/uL*
HGB	*12.5 - 16.3 g/dL*
HCT	*37.1 - 49.5 %*
PLT	*152 - 440 K/uL*
MCV	*79.0 - 97.0 fL*
MCH	*26.2 - 32.0 pg*
MCHC	*33.3 - 35.7 g/dL*
RDW	*12.1 - 16.0 %*
MPV	*7.0 - 10.8 fl*
NRBC	*0.00 /100 WBCs*
ABSOLUTE NRBC	*K/uL*
NEUTS	*46.5 - 82.4 %*
EOSINOPHIL	*0.1 - 6.0 %*
BASOPHIL	*0.1 - 1.1 %*
LYMPHS	*8.5 - 32.7 %*
MONOS	*5.4 - 14.2 %*
ABSOLUTE NEUTS	*2.23 - 6.11 K/uL*
ABSOLUTE EOS	*0.00 - 0.52 K/uL*
ABSOLUTE BASO	*0.00 - 0.11 K/uL*
ABSOLUTE LYMPHS	*0.21 - 2.74 K/uL*
ABSOLUTE MONOS	*0.2 - 0.87 K/uL*

COMPREHENSIVE METABOLIC PANEL	*Normal Range*
SODIUM	*135 - 145 mmol/L*
POTASSIUM	*3.5 - 5.0 mmol/L*
CHLORIDE	*98 - 108 mmol/L*
CO2	*23 - 32 mmol/L*
BUN	*9 - 25 mg/dL*
CREATININE	*0.7 - 1.3 mg/dL*
GLUCOSE	*70 - 100 mg/dL*
ALBUMIN	*3.7 - 5.4 g/dL*
TOTAL PROTEIN	*6.0 - 8.0 g/dL*
CALCIUM	*8.8 - 10.5 mg/dL*
ALKALINE PHOSPHATASE	*36 - 118 U/L*
TOTAL BILIRUBIN	*0.2 - 1.2 mg/dL*
AST	*9 - 30 U/L*
ALT	*7 - 52 U/L*
GLOBULIN	*2.3 - 4.2 g/dL*
EGFR	*>59 mL/min/1.73m2*
ANION GAP	*5 - 17 mmol/L*

OTHER STANDARD GvHD	Normal Range
TACROLIMUS	3.0 - 15.0 ng/mL
VITAMIN D Total, 25-OH (D2 and D3) Sunquest Lab, OHDT	20-80 ng/mL
T4 (thyroxine), Total, Serum	11 -19 years: 5.9-13.2 µg/dL Adult (> or =20 years): 4.5-11.7 µg/dL
T4 (thyroxine), Free, Serum	11-19 years: 1.0-1.6 ng/dL Adult (> or =20 years): 0.9-1.7 ng/dL
T3 (triodothyronine), Total, Serum	11-19 years: 91-218 ng/dL Adult (> or =20 years): 80-200 ng/dL
ACTH (adrenocorticotropic hormone), Plasma	7.2-63 pg/mL (a.m. draws)
TSH (thyroid stimulating hormone), Serum	0.27 - 4.20 µIU/mL

ENDOCRINE PANEL	Normal Range
DHEA-S (dehydroepiandrosterone sulfate), Serum	18-30 years: 105-728 µg/dL 31-40 years: 57-522 µg/dL 41-50 years: 34-395 µg/dL 51-60 years: 20-299 µg/dL 61-70 years: 12-227 µg/dL > or =71 years: 6.6-162 µg/dL
ESTRADIOL, Serum	Follicular Phase 27-156 pg/mL Mid Cycle Peak 48-314 pg/mL Luteal Phase 33-298 pg/mL Postmenopausal <50 pg/mL
FSH (follicle stimulating hormone), Serum	Male 1.6-8.0 mIU/mL Female Follicular Phase 2.5-10.2 mIU/mL Mid-Cycle Peak 3.1-17.7 mIU/mL Luteal Phase 1.5- 9.1 mIU/mL Postmenopausal 23.0-116.3 mIU/mL
LH (luteinizing hormone), Serum	Male 18-59 Years 1.5-9.3 mIU/mL ≥60 Years 1.6-15.2 mIU/mL Female Follicular Phase 1.9-12.5 mIU/mL Mid-Cycle Peak 8.7-76.3 mIU/mL Luteal Phase 0.5-16.9 mIU/mL Postmenopausal 10.0-54.7 mIU/mL
PTH (Parathyroid Hormone), Serum	15-65 pg/mL
PROGESTERONE, Serum	MALES > or =18 year: <0.20 ng/mL FEMALES > or =18 years: -Follicular phase: < or =0.89 ng/mL -Ovulation: < or =12 ng/mL -Luteal phase: 1.8-24 ng/mL -Post-menopausal: < or =0.20 ng/mL -Pregnancy - 1st trimester: 11-44 ng/mL - 2nd trimester: 25-83 ng/mL

ENDOCRINE PANEL	Normal Range
	- 3rd trimester: 58-214 ng/mL
TESTOSTERONE, Total and Free, Serum Mayo Clinic test code TGRP	TESTOSTERONE, FREE Males (adult): 20-<25 years: 5.25-20.7 ng/dL 25-<30 years: 5.05-19.8 ng/dL 30-<35 years: 4.85-19.0 ng/dL 35-<40 years: 4.65-18.1 ng/dL 40-<45 years: 4.46-17.1 ng/dL 45-<50 years: 4.26-16.4 ng/dL 50-<55 years: 4.06-15.6 ng/dL 55-<60 years: 3.87-14.7 ng/dL 60-<65 years: 3.67-13.9 ng/dL 65-<70 years: 3.47-13.0 ng/dL 70-<75 years: 3.28-12.2 ng/dL 75-<80 years: 3.08-11.3 ng/dL 80-<85 years: 2.88-10.5 ng/dL 85-<90 years: 2.69-9.61 ng/dL 90-<95 years: 2.49-8.76 ng/dL 95-100+ years: 2.29-7.91 ng/dL Females (adult): 20-<25 years: 0.06-1.08 ng/dL 25-<30 years: 0.06-1.06 ng/dL 30-<35 years: 0.06-1.03 ng/dL 35-<40 years: 0.06-1.00 ng/dL 40-<45 years: 0.06-0.98 ng/dL 45-<50 years: 0.06-0.95 ng/dL 50-<55 years: 0.06-0.92 ng/dL 55-<60 years: 0.06-0.90 ng/dL 60-<65 years: 0.06-0.87 ng/dL 65-<70 years: 0.06-0.84 ng/dL 70-<75 years: 0.06-0.82 ng/dL 75-<80 years: 0.06-0.79 ng/dL 80-<85 years: 0.06-0.76 ng/dL 85-<90 years: 0.06-0.73 ng/dL 90-<95 years: 0.06-0.71 ng/dL 95-100+ years: 0.06-0.68 ng/dL TESTOSTERONE, TOTAL Males 17-18 years: 300-1,200 ng/dL > or =19 years: 240-950 ng/dL Females 17-18 years: 20-75 ng/dL > or =19 years: 8-60 ng/dL

Initials: _____ Subject #:_____

Home Record of Actual Ocular Medication and Artificial Tear Use

(Record date and number of times used per day and night)

	GV-1	**Ocular Med 1**	**Ocular Med 2**	**Artificial Tears & Gels**	**Artificial Tears & Gels**	**Ocular Med 4**	**Ocular Med 5**	**Ocular Med 6**
				Use only when necessary				
Name of medication								
Date								

GLIA OCULAR SURFACE DISEASE SYMPTOMS QUESTIONNAIRE - DIARY

DATE: _____ DAY OF WEEK: _____

Initials: _____ Subject #: _____ Reviewed by / date: _____

Grade by placing X on the line from 'None' to 'Most severe' None _____ Most

	Baseline Time: _____	
	OD	**OS**
Ocular discomfort	None _____ Most	None _____ Most
Dryness	None _____ Most	None _____ Most
Grittiness	None _____ Most	None _____ Most
Burning	None _____ Most	None _____ Most
Stinging	None _____ Most	None _____ Most
Foreign body sensation	None _____ Most	None _____ Most
Ocular pain	None _____ Most	None _____ Most
Conjunctival redness	None _____ Most	None _____ Most
Itching	None _____ Most	None _____ Most
Mucus discharge	None _____ Most	None _____ Most
Photophobia	None _____ Most	None _____ Most
Blurred or cloudy vision	None _____ Most	None _____ Most
Airflow sensitivity	None _____ Most	None _____ Most
Lid redness	None _____ Most	None _____ Most
Lid sticking	None _____ Most	None _____ Most

Additional notes below: (Details and other ocular symptoms)

Initials: _____ Subject #:_____

ADVERSE EVENT LOG

Visit Number	Report date (mm/dd/yyyy)	Adverse event	Relationship to study drug(1, 2, or 3)	Adverse event onset date (mm/dd/yyyy)	Adverse event end date (mm/dd/yyyy)	Severity (1, 2,or 3)	Action taken with study drug(1-, 2, 3, or 4)	Specify, if action taken with study drug="4. Other"	Outcome (1, 2,or 3)	Serious adverse event (Yes/No)

Enter numerical responses for following Questionnaire categories

Relationship to study drug:

1. None
2. Possibly related
3. Probably related

Severity:

1. Mild
2. Moderate
3. Severe

Action taken with study drug:

1. None
2. Permanently Discontinued*
3. Temporarily Discontinued
4. Other(specify)

Outcome:

1. Resolved
2. Ongoing
3. Lost to follow-up

*** Complete study discontinuation form**